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<b>(54) Title:</b> METHODS AND COMPOSITIONS FOR THE PREVENTION AND TREATMENT OF MUSCLE CRAMPS AND IMPROVING MUSCULAR STRENGTH IN ATHLETES		
<b>(57) Abstract</b>  The present invention relates to methods and compositions for the prevention and/or treatment of exercise-induced muscle cramps, stiffness, pain or spasms, using magnesium gluconate alone or in combination with one or more antioxidants or conventional pharmacologic therapy. The invention also relates to inhibition of production of oxygenated molecules, oxygen free radicals and lipid peroxidation.  <div style="text-align: right;"><i>in antioxidants</i></div>		

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**METHODS AND COMPOSITIONS FOR THE  
PREVENTION AND TREATMENT OF MUSCLE CRAMPS  
AND IMPROVING MUSCULAR STRENGTH IN ATHLETES**

The present application is a Continuation-in-Part of Application Serial  
5 No. 08/588,564 filed January 18, 1996, which is incorporated by reference herein in  
its entirety.

**1. INTRODUCTION**

The present invention relates to methods and compositions for the  
prevention and treatment of muscle cramps, stiffness, pain and spasms and for  
10 improving muscular strength. The methods and compositions of the invention are  
especially suitable for parenteral or enteral administration and are useful in preventing  
and/or treating neuromuscular problems and exercise-induced muscle cramps or free  
radicals in muscle.

**2. BACKGROUND OF THE INVENTION**

15 **2.1 Exercise-Induced Muscle Trauma**

Many sports put the participants at risk of direct trauma to muscle,  
tendon, ligament and subcutaneous tissues, e.g., by contact with the ground, the  
opponent, a ball or a bat. Much of the pain and disability resulting from soft-tissue  
trauma is due not to the injury itself but to bleeding in and around the damaged tissue.  
20 Extravasated blood causes pain by limiting movement and by local inflammation  
caused by pro-inflammatory mediators.

Magnesium homeostasis is essential to good health and proper neuromuscular  
function and magnesium deficiency may result in neuromuscular problems such as  
muscle cramps, stiffness, pain and spasms. For most athletes performing strenuous  
25 exercise, magnesium may be lost from the body. Sweating appears to account for  
some of this loss. McDonald, R., et. al., 1988, *Sports Med.*, 5: 171-184.

However, most magnesium is lost via urinary excretion after exercise, which may

be due to metabolic acidosis and increases in aldosterone and antidiuretic hormone.

Rayssiguier, Y. et. al., 1990, *Magnesium Res.*, 3: 93-102.

## 2.2 Neuromuscular Effects

The neuromuscular effects of hypomagnesemia occur commonly in association with hypocalcemia and/or hypokalemia-although the symptoms and signs may be seen in the absence of any other electrolyte abnormalities. Hypomagnesemia associated neuromuscular abnormalities include Trousseau's or Chvostek's signs, tetany, muscle fasciculation, tremor, muscle spasticity, deep tendon reflexes, anxiety, delirium, grand mal seizures, nystagmus, ataxia, vertigo, choreoathetoid movements and dysphagia. Almost all conditions resolve quickly with magnesium replacement. Ntoso, K.A and Goldfarb, S., in *Internal Medicine* ed. J.H. Stein, 2345-2349, Little, Brown and Company, Inc., (1990). In adolescence, magnesium deficiency may also be associated with muscle pain, early fatigue and stiffness, growing pains and/or Osgood-Schlatter's disease or cramps on strenuous exertion in patients having muscle glycogenoses, Chen, Y-T, in *Internal Medicine*, ed. W.N. Kelley, 2270-2273 J.B. Lippincott (1992).

## 2.3 Magnesium

Magnesium is an important element for health and disease. It is the fourth most abundant cation in the human body and is the second most abundant intracellular cation. Elin, R.J., 1987, *Clin. Chem.*, 33: 1965-1970. Magnesium is a cofactor for approximately 300 enzymes and is essential for energy metabolism and for protein and nucleic acid synthesis. Magnesium deficiency may result from a number of factors including decreased intake or increased gastrointestinal or renal loss of magnesium, drug therapy, and alterations in magnesium distribution. Hypomagnesemia is generally defined as a serum magnesium concentration of less than 1.5 mEq/l. The signs and symptoms of hypomagnesemia include arrhythmias, electrocardiographic changes, hypertension, depression, delirium, agitation, tetany,

leg cramps, tremors, ataxia, weakness, confusion and convulsions. The ideal intake of magnesium for an adult is 15 to 20 mM/d (350 to 450 mg/d). Magnesium is absorbed primarily in the jejunum and ileum, and healthy persons absorb about 30 to 40 percent of ingested magnesium. The majority of adults have a dietary intake of magnesium  
5 less than the recommended dietary allowance (RDA) in the range of 43 to 93.0 percent of RDA. Pao, E.M., Micke, S.J., 1981, *Food Technol.*, 35: 58-69.

Magnesium functions in a wide range of biochemical and physiological processes. Inside cells, magnesium serves as a modulator of many rate limiting enzymes. Extracellular levels of magnesium play an important role in muscle and  
10 nerve excitability by maintaining electrical potentials at the membrane. National Research Council, *Recommended Dietary Allowances*, 10th ed. Washington, D.C.: National Academy Press, 1989, pp. 1, 10-23, 174-205.

### 3. SUMMARY OF THE INVENTION

The present invention relates to methods and compositions for the  
15 prevention and treatment of muscle cramps, stiffness, pain and spasms, utilizing an effective amount of magnesium gluconate. The methods and compositions of the invention are especially useful in preventing and/or treating neuromuscular problems and exercise-induced muscle cramps or free radicals in muscle.

The present invention also relates to methods and compositions for  
20 improving muscle strength.

The present invention also contemplates the prevention and treatment of muscle cramps, stiffness, pain and spasms using an effective amount of magnesium gluconate along with conventional therapy for such conditions.

The present invention also provides a method for treating and/or  
25 preventing neuromuscular problems and damage caused by inflammatory reactions and/or oxygen free radicals, by providing a therapeutically effective amount of magnesium gluconate.

The present invention also provides a method for improving muscular strength in a human subject by using an effective amount of magnesium gluconate.

#### 4. DESCRIPTION OF THE FIGURES

Figure 1. Effects of magnesium salts on free radical mediated  
5 membrane lipid peroxidation.

Figure 2. Effect of magnesium salts on site-specific  $\text{OH}^\bullet$ -mediated deoxyribose oxidation.

Figure 3. Effect of magnesium salts on  $\text{R}_1$ -induced loss of BA-endothelial cell glutathione.

10 Figure 4. Effect of magnesium salts on  $\text{R}_1$ -induced loss of endothelial cell proliferation.

#### 5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods and compositions for the prevention and treatment of muscle cramps, stiffness, pain and spasms. The present  
15 invention also provides a method for treating and/or preventing neuromuscular problems and exercise-induced muscle cramps or free radicals in muscles of athletes.

Neuromuscular problems or abnormalities associated with hypomagnesemia also include Trousseau's or Chvostek's signs, tetany, muscle fasciculation, tremor, muscle spasticity, deep tendon reflexes, anxiety, delirium, grand  
20 mal seizures, nystagmus, ataxia, vertigo, choreoathetoid movements or dysphagia. Other muscle conditions associated with magnesium deficiency especially in adolescence, include muscle pain, early fatigue and stiffness, growing pains and/or Osgood-Schlatter's disease or cramps on strenuous exertion.

The invention also provides a method for treating and/or preventing  
25 inflammatory reactions and inhibiting production of oxygen free radicals during strenuous exercise in athletes.

The present invention is also directed to a method for the prevention and treatment of muscle cramps, stiffness, pain and spasms using an effective amount of magnesium gluconate along with conventional therapy for such conditions.

5 The invention also provides a method for improving muscular strength in a human subject.

The present invention further relates to compositions containing magnesium gluconate in combination with antioxidants such as vitamin E, selenium, glutathione, glutathione isopropyl ester, or N-acetylcysteine, for use in the prevention and/or treatment of muscle cramps, stiffness, pain and spasms, and for improving  
10 muscular strength in a human subject.

"Conventional therapy" for muscle cramps and related conditions, as used herein includes muscle relaxants (e.g. diazepam) or anti-inflammatory agents (e.g. ibuprofen).

"Oxygen free radical" as used herein refers to a free radical molecule  
15 with an odd, unpaired electron which makes the molecule unstable and highly reactive. Tribble, D.L., et. al., 1987, *Hepatology*, 7: 377-386. Small amounts of these free radicals are produced endogenously by the mitochondrial electron transport system and the endoplasmic reticulum in microsomes and peroxisomes. Oxygen free radicals, the superoxide anion ( $O_2^-$ ) the hydroxyl radical ( $^{\circ}OH$ ), and their  
20 intermediary, hydrogen peroxide ( $H_2O_2$ ) are believed to be generated in vascular complications associated with exercise-induced muscle cramps, stiffness, pain or spasms, e.g., platelet aggregation, vasoconstriction and bronchoconstriction. The free radicals interact with other cellular constituents such as deoxyribonucleic acid (DNA) and lipids and lead to subsequent formation of multiple degradation products. Lipid  
25 peroxidation forms lipid peroxides and aldehydes that interact with protein sulfhydryl groups and thereby perpetuate cellular damage. Del Maestro, R.F., 1980, *Acta. Physiol. Scand.*, 492 (Suppl.): 153-168.

Normally, protective mechanisms are present in the cell to prevent damage by free radicals. For example, the primary mechanism of clearance of  $O_2^{\cdot -}$  from biologic systems is superoxide dismutase, which catalyses the dismutation of  $O_2^{\cdot -}$  to  $H_2O_2$  and  $O_2$ . The cytoplasmic enzymes glutathione peroxidase and catalase provide the final detoxification steps with the reduction of  $H_2O_2$  to  $O_2^{\cdot -}$ . Glutathione peroxidase seems to be a more active enzyme than catalase in protecting cells such as myocardial cells or endothelial cells from  $H_2O_2$ -mediated damage. Fridovich, I., 1983, *Annu. Rev. Pharmacol. Toxicol.*, 23: 239-257; Fantone, J.C., et. al., 1982, *Am. J. Pathol.*, 107: 395-418.

10           The present invention provides a method comprising administering to a human subject at risk of exercise-induced muscle cramps, stiffness, pain or spasms, a composition comprising magnesium gluconate in sufficient amounts to inhibit oxygen free radical production and lipid peroxidation.

          In different embodiments of the invention, the composition of the invention may be administered enterally or parenterally in the prevention or treatment of muscle cramps, stiffness, pain or spasms and in improving muscle strength.

          The compositions of the invention may comprise tablets, capsules, powder preparations, aqueous solutions and nutrient preparations containing magnesium gluconate in an amount sufficient to inhibit oxygen free radical production and lipid peroxidation in various vascular and membrane tissues.

          Administration of magnesium gluconate results in cellular resistance to oxygen free radical stress and free radical production, for example lipid peroxides.

          Magnesium is an important metallo coenzyme for many enzyme reactions. In the method of the present invention, magnesium gluconate inhibits the production of free radicals, reduces cellular damage due to oxidative stress, reduces lipid peroxidation and reduces glutathione loss.

          Spontaneous or exercise-related discomfort from muscles is usually benign and does not signal chronic disease. The terms cramp, pain and spasm are



often used interchangeably to describe symptoms referred to muscles. Other terms, such as aching and stiffness are also used.

"Cramp" as used herein, refers to a spontaneous, prolonged and painful contraction of one or more muscles. Muscle pain may be associated with strenuous exercise or fatigue. Cramping or muscle spasm is a common complaint in athletes and has multiple causes. There is a distinction between the cramp that occurs with effort or injury and the cramp that occurs at rest at night (nocturnal cramp). Cramps in athletes may occur during exercise when a relative arterial insufficiency in blood flow arises or when transient ischemia caused by isometric contractions in overused muscle groups occurs. Injury to the muscle, by a blow that causes slight infiltration of blood, overstretching of a muscle with resultant tearing of some fibers, or strain by overcontraction of the muscle against resistance frequently leads to muscle cramps or spasm. Some cramps may appear without warning and without any apparent etiology. In a hot climate overheating, or excessive sweating leading to a decrease in body electrolyte content, may cause muscle spasm. Sudden chilling may cause cramping or spasm. A build-up of carbondioxide or lactic acid in the muscle and a decrease in oxygenation may also cause cramping. R.E. Rakel, ed. Textbook of Family Practice, 3rd ed., W.B. Saunders Co., 691-692 (1984).

"Spasm" as used herein, refers to a brief, unsustained abnormal contraction of a single or multiple muscles. Abnormal movements of muscle may arise from abnormal electrical activity of the central nervous system mediated via the motor neuron or muscle fiber itself.

#### **5.1 Effects of Exercise on Magnesium Status and Muscular Strength**

Although magnesium status may not appear to be compromised, there are several reports showing that magnesium may be lost from the body after performing strenuous exercise and the reduced levels may be undetectable by blood chemistry. Blood levels of magnesium are altered by exercise. For example, serum levels of magnesium were found to be significantly lower than baseline after thirty

minutes of swimming (Laires, M.J., et. al., 1991, *Magnes. Res.*, 4: 119-122), after a 120-km hike (Stendig-Lindberg, G.Y., et. al., 1988, *Am. J. Coll. Nutr.*, 6: 35-40), after a marathon race in eight runners (Rose, L.I., et. al., 1970, *J. Appl. Physiol.*, 29: 449-451), and after high-intensity anaerobic treadmill running in thirteen men (Deuster, P.A., et. al., 1987, *J. Appl. Physiol.*, 62: 545-550).

However, these losses appear to be made up by the diet after extended periods of time (Stendig-Lindberg, G.Y., et. al., 1988, *Am. J. Coll. Nutr.*, 6: 35-40), because most athletes do not show a compromised magnesium status.

Magnesium homeostasis is essential to good health and proper neuromuscular function and magnesium deficiency may result in neuromuscular problems such as muscle cramps, stiffness, pain and spasms.

The rate of cellular respiration increases during exercise in order to facilitate oxygen delivery to the working muscle. In cellular respiration, during reduction of the molecular oxygen to water, partially reduced oxygen species are produced that are very reactive with protein, lipids, and DNA, producing deleterious effects and damage on cells by peroxidation of lipids. Janssen, Y.M., et. al., 1993, *Lab. Invest.*, 69: 261-274. Since the reduction of molecular oxygen to water in the electron transport chain increases in contracting muscle, more oxygen free radicals are formed during exercise. Thus, exercise-induced free radicals may cause damage to mitochondrial membranes in a chronic training situation. Davies, K.J.A., et. al., 1982, *Biochem. Biophys. Res. Commun.*, 107: 1198-1205.

The exact nature of the relationship between magnesium and muscle strength or exercise-induced muscle cramps, stiffness, pain or spasms remains to be explained. However, the compositions and methods of the present invention are especially suited for use in improving muscle strength and in the treatment and prevention of exercise-induced muscle cramps, stiffness, pain or spasms by virtue of their enhanced properties as antioxidants compared with other magnesium salts as

described *infra*, in Section 6, and by virtue of having minimal purgative action on the gut.

## 5.2 Pharmaceutical Preparations and Methods of Administration

Magnesium gluconate compositions for use in accordance with the present invention are formulated by mixing magnesium gluconate into an aqueous solution or by mixing a suitable magnesium salt, for example, magnesium carbonate, with glucono-delta-lactone or magnesium carbonate with glucono-delta-lactone and/or citric acid. Desirably, the following concentrations are utilized: magnesium carbonate in the range of 2mg per liter to 44g per liter; citric acid in the range of 2.3mg. per liter to 46.2g per liter; and glucono-delta-lactone in the range of 6mg per liter to 26 mg per liter. There results an aqueous solution of magnesium gluconate or magnesium gluconate/citrate, i.e., a solution containing magnesium gluconate and magnesium citrate that exerts unexpected and stronger antioxidant, antiperoxidative and cytoprotective effects than other magnesium salts, as described more fully in Section 7.0 below. In addition, magnesium gluconate may be included in a nutritional formula or in the form of tablets, capsules and powdered or granular preparations which are reconstituted to provide an aqueous composition.

Aqueous magnesium gluconate compositions of the invention comprise formulations suitable for enteral, parenteral and rectal administration.

The compositions of the present invention for preventing and/or treating exercise-induced muscle cramps, stiffness, pain or spasms, should be administered to a patient at therapeutically effective doses. A therapeutically effective dose refers to that amount of the magnesium compound sufficient to result in the amelioration of symptoms of exercise-induced muscle cramps, stiffness, pain or spasms. Similarly, a therapeutically effective dose refers to that amount of the antioxidants, including but not limited to, Vitamin E, selenium, glutathione, glutathione isopropyl ester or N-acetylcysteine, sufficient to result in the amelioration of symptoms of exercise-induced muscle cramps, stiffness, pain or spasms.

Toxicity and therapeutic efficacy of the magnesium compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% in the population). The dose ratio  
5 between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosages for use in humans.

### 5.3 Formulations

10 Magnesium gluconate compositions for use in accordance with the present invention are formulated by mixing magnesium gluconate into an aqueous solution or by mixing a suitable magnesium salt, for example, magnesium carbonate, with glucono-delta-lactone or magnesium carbonate with glucono-delta-lactone and/or citric acid. Pharmaceutical compositions for use in accordance with the present  
15 invention can be formulated by conventional means in aqueous form, powdered preparations or by using one or more physiologically acceptable carriers, excipients or buffers.

Thus, the compounds and their physiologically acceptable salts and solvates can be formulated for administration by insufflation (either through the  
20 mouth or the nose) or oral, buccal, parenteral or rectal administration.

For oral administration, the pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g.,  
25 lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate or talc); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can

take the form of, for example, aqueous solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydrobenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate. The preparations can also take the form of powdered preparations or nutritional formulas.

Preparations for oral administration can be formulated to give controlled release of the active compound.

For buccal administration the compositions can take the form of tablets or lozenges formulated in the conventional manner.

The compounds can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, other glycerides or carbowaxes.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by

intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

5                   The compositions can, if desired, be presented in a pack or dispenser device which can contain one or more unit dosage forms containing the active ingredient. The pack can for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration.

10                   Patient dosages for enteral or parenteral administration range from 10 to 150 mEq of magnesium gluconate per day, commonly 20-50 mEq per day, and typically from 20 to 30 mEq per day. Stated in terms of milligrams of Mg, dosages range from 100 mg per day to 1800 mg per day, commonly 250 mg to 600mg per day.

                  Dosage amounts of antioxidants for enteral administration range from  
15   for example, for vitamin E: 200 to 1000 I.U. per day. Dosage amount and interval may be adjusted to provide plasma levels which are sufficient to maintain normal metabolism.

## 6.           EXAMPLE

                  The antioxidant properties of magnesium gluconate were studied by  
20   incubating microsomal membranes prepared from endothelial cells in the presence of 0.25, 0.5, 1.0 and 2.0 mM of magnesium salts including magnesium gluconate, magnesium sulfate and magnesium chloride or sodium gluconate. Membrane malondialdehyde and site specific OH<sup>-</sup>-mediated deoxyribose oxidation were measured according to methods described by Mak, I.T. & Weglicki, W.B., 1994,  
25   *Method Enzymol.*, 234: 620-630; and Mak, I.T. et. al., 1990, *Biochem. Pharm.*, 40: 2169-2175. Results demonstrate that magnesium gluconate is more effective than magnesium sulfate or sodium gluconate in inhibiting free radical production (e.g.,

malondialdehyde which also indicates TXA<sub>2</sub> production) (Figure 1). Magnesium gluconate is also more effective than magnesium chloride or magnesium sulfate in inhibiting free radical mediated deoxyribose oxidation in a dose-related manner. (Figure 2). These data indicate magnesium gluconate has unexpected and more powerful antioxidant properties and thromboxane inhibiting activity than other magnesium salts.

Cultured bovine aortic (BA) endothelial cells were incubated with R. (R.= 0.83 mM dihydroxyfumarate + 0.025mM Fe<sup>3+</sup> -ADP) for 50 mins at 37°C. Glutathione (GSH) was then determined by the enzymatic method described by Mak, I.T., et. al., 1992, *Cir. Res.*, 70: 1099-1103. A loss of 56% of total GSH was observed. When the cells were pretreated for 10 mins with varying amounts of magnesium gluconate or magnesium sulfate before being exposed to R., magnesium gluconate significantly prevented the GSH loss to varying degrees (p<0.05). The EC50 was 1.1 mM (Figure 3).

When endothelial monolayers (about 65% confluent) were incubated with R. for 30 min, the cell survival/proliferation determined by the tetrazolium salt MTT assay (Mak, I.T., et. al., 1995, *Biochem. Pharmacol.*, 50: 1531-1534), decreased to 38% of control at 24 hr. Pretreatment with magnesium gluconate attenuated the loss in cell survival/proliferation (expressed as % of control (cont.)) in a dose-dependent manner compared with the cells pretreated with magnesium sulfate (Figure 4).

It is important to note that the effects of magnesium sulfate on R.-induced loss of GSH or R.-induced losses of cell survival/proliferation were much lower than those obtained with magnesium gluconate, i.e., magnesium sulfate was approximately 33% as potent as magnesium gluconate (Figs 1-4).

7. **EXAMPLE: USE OF MAGNESIUM GLUCONATE IN EXERCISE-INDUCED MUSCLE CRAMPS**

The invention is illustrated, by way of protocols for exercise-induced muscle cramping in men over 35 years of age who experience muscle cramps, stiffness and pain during rugby playing.

The efficacy of oral magnesium gluconate (Magonate® - Fleming and Co., Pharmaceuticals) is compared with a matching placebo, sodium gluconate. 30mL magnesium (324mg Mg) is given before the start of a rugby game in 25 subjects. The magnesium status of each subject in the study is evaluated by measuring serum magnesium, erythrocyte magnesium concentrations, leukocyte magnesium concentration or 24-hour magnesium excretion before the start of the rugby game and after the game. Thus, there is a pre-game magnesium status measured for each subject. Each subject is used to test the effect of the placebo at the following rugby game. The methods employed to measure magnesium include use of ion-selective electrodes and nuclear magnetic resonance spectroscopy, as described by Elin, R.J., 1987, *Clin. Chem.*, 33: 1965-1970; and Deuster, P.A. et. al., 1987, *Clin. Chem.*, 33: 529-532; and Bardicof, M., et. al., 1995, *Am. J. Obstet. Gynecol.*, 172: 1009-1013.

Each subject is interviewed immediately post-game and the following information is recorded: cramping information (number, intensity, location, duration, amount of time cramping caused the subject to stop playing) and muscle pain or stiffness (frequency, intensity, location and duration).

The number of occurrences of cramps, pain or stiffness are reduced when the subjects receive magnesium gluconate before the start of the game as compared with when they receive sodium gluconate. Thus, the magnesium gluconate compositions of the present invention are useful in the prevention and/or treatment of muscle cramping, pain or stiffness.



The present invention is not to be construed as limited in scope to the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such

5    modifications are intended to fall within the scope of the appended claims.

## WHAT IS CLAIMED IS:

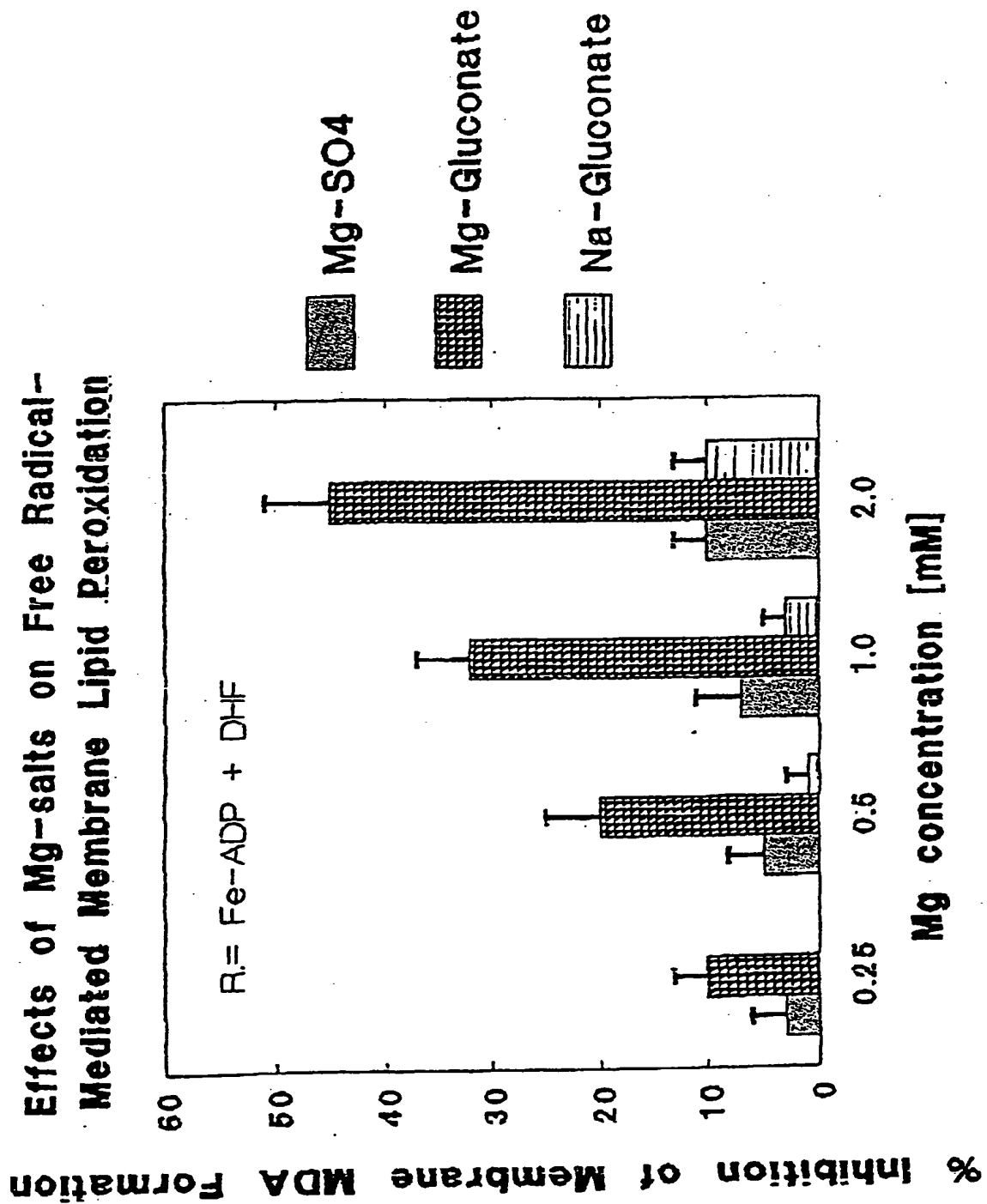
1. A method for preventing or treating exercise-induced muscle cramps, stiffness, pain or spasms in a human subject, the method comprising administering to the human subject undertaking such exercise a therapeutically effective amount of magnesium gluconate.  
5
2. A method for preventing or treating exercise-induced muscle cramps, stiffness, pain or spasms caused by or related to production of oxygen free radicals in a human subject, the method comprising administering to the human subject an effective amount of magnesium gluconate.
- 10 3. The method of claim 2, wherein the magnesium gluconate is at a concentration range of approximately 0.1 mM to 1.5 M.
4. The method of claim 2, wherein the magnesium gluconate is administered enterally.
5. The method of claim 2, wherein the magnesium gluconate is administered  
15 parenterally.
6. The method of claim 2, wherein the magnesium gluconate is administered rectally.
7. The method of claim 2 further comprising administering a pharmaceutical agent selected from the group consisting of a muscle relaxant or an anti-  
20 inflammatory agent.
8. The method of claim 2 further comprising administering one or more antioxidants selected from the group consisting of vitamin E, selenium, glutathione, glutathione isopropyl ester and N-acetylcysteine.

9. The method of claim 7 further comprising administering one or more antioxidants selected from the group consisting of vitamin E, selenium, glutathione, glutathione isopropyl ester and N-acetylcysteine.
10. A composition suitable for administering to a human subject for the  
5 prevention or treatment of exercise-induced muscle cramps, stiffness, pain or spasms, said composition comprising magnesium gluconate and an antioxidant selected from the group consisting of vitamin E, selenium, glutathione, glutathione isopropyl ester and N-acetylcysteine.
11. The composition of claim 10, wherein the magnesium gluconate is in the  
10 range from about 0.1 mM to about 1.5 M.
12. The composition of claim 10, wherein the concentration of magnesium gluconate is sufficient to treat or prevent exercise-induced muscle cramps, stiffness, pain or spasms related to production of oxygen free radicals and lipid peroxidation.
13. A method for preventing or treating neuromuscular conditions, the method  
15 comprising administering to a human subject a therapeutically effective amount of magnesium gluconate.
14. The method of claim 13, wherein the magnesium gluconate is at a concentration range of approximately 0.1mM to 1.5M.
15. The method of claim 14 wherein the magnesium gluconate is administered  
20 enterally, parenterally or rectally.
16. The method of claim 15, wherein the neuromuscular conditions comprise Trousseau's or Chvostek's signs, tetany, muscle fasciculation, tremor, muscle spasticity, deep tendon reflexes, anxiety, delirium, grand mal seizures, Nystagmus, ataxia, vertigo, choreoathetoid movements or dysphagia.

17. The method of claim 13 further comprising administering one or more antioxidants selected from the group consisting of vitamin E, selenium, glutathione, glutathione isopropyl ester and N-acetylcysteine.
18. The method of claim 17, wherein the neuromuscular conditions comprise
- 5 Trousseau's or Chvostek's signs, tetany, muscle fasciculation, tremor, muscle spasticity, deep tendon reflexes, anxiety, delirium, grand mal seizures, Nystagmus, ataxia, vertigo, choreoathetoid movements or dysphagia.
19. A composition suitable for administering to a human subject for the prevention or treatment of neuromuscular conditions, said composition comprising
- 10 magnesium gluconate and an antioxidant selected from the group consisting of vitamin E, selenium, glutathione, glutathione isopropyl ester and N-acetylcysteine.
20. The composition of claim 17, wherein the magnesium gluconate is in the range from about 0.1mM to about 1.5M.

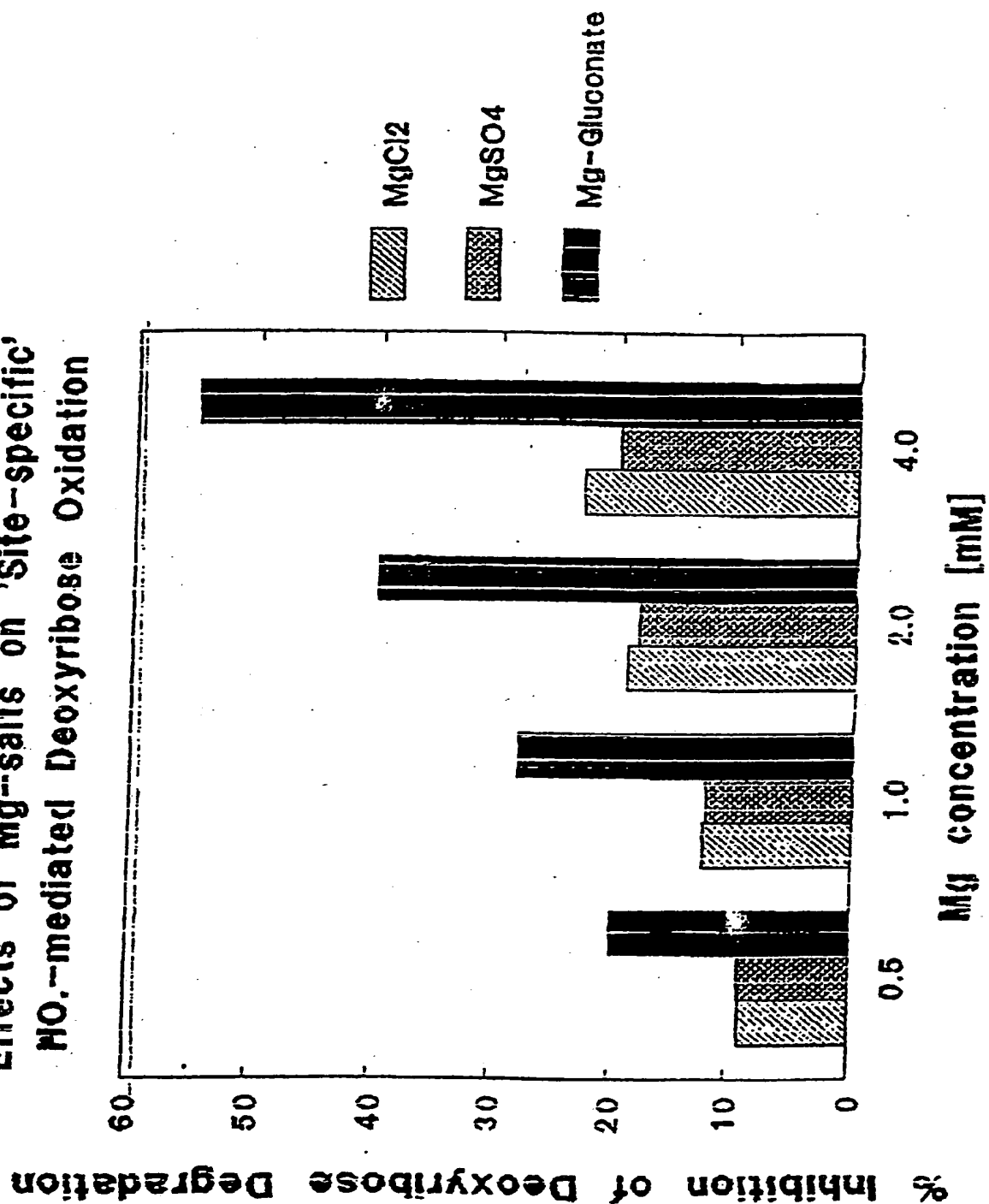
1/4

FIGURE 1.



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**Effects of Mg--salts on 'Site-specific'  
HO<sub>2</sub>--mediated Deoxyribose Oxidation**



3/4

FIGURE 3.  
Effects of Mg-Gluconate & MgSO<sub>4</sub> on  
R.-induced loss of BA-EC Glutathione

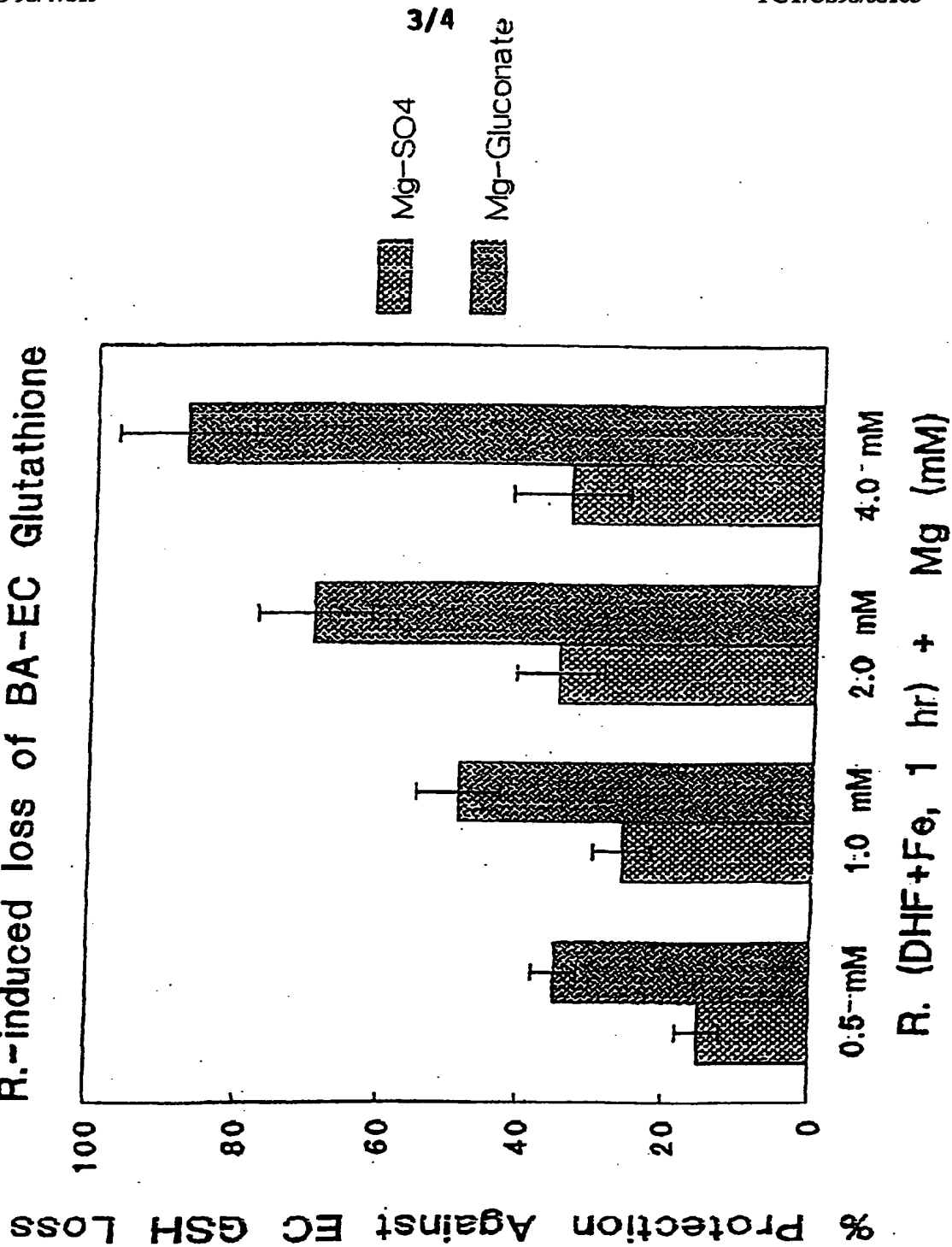
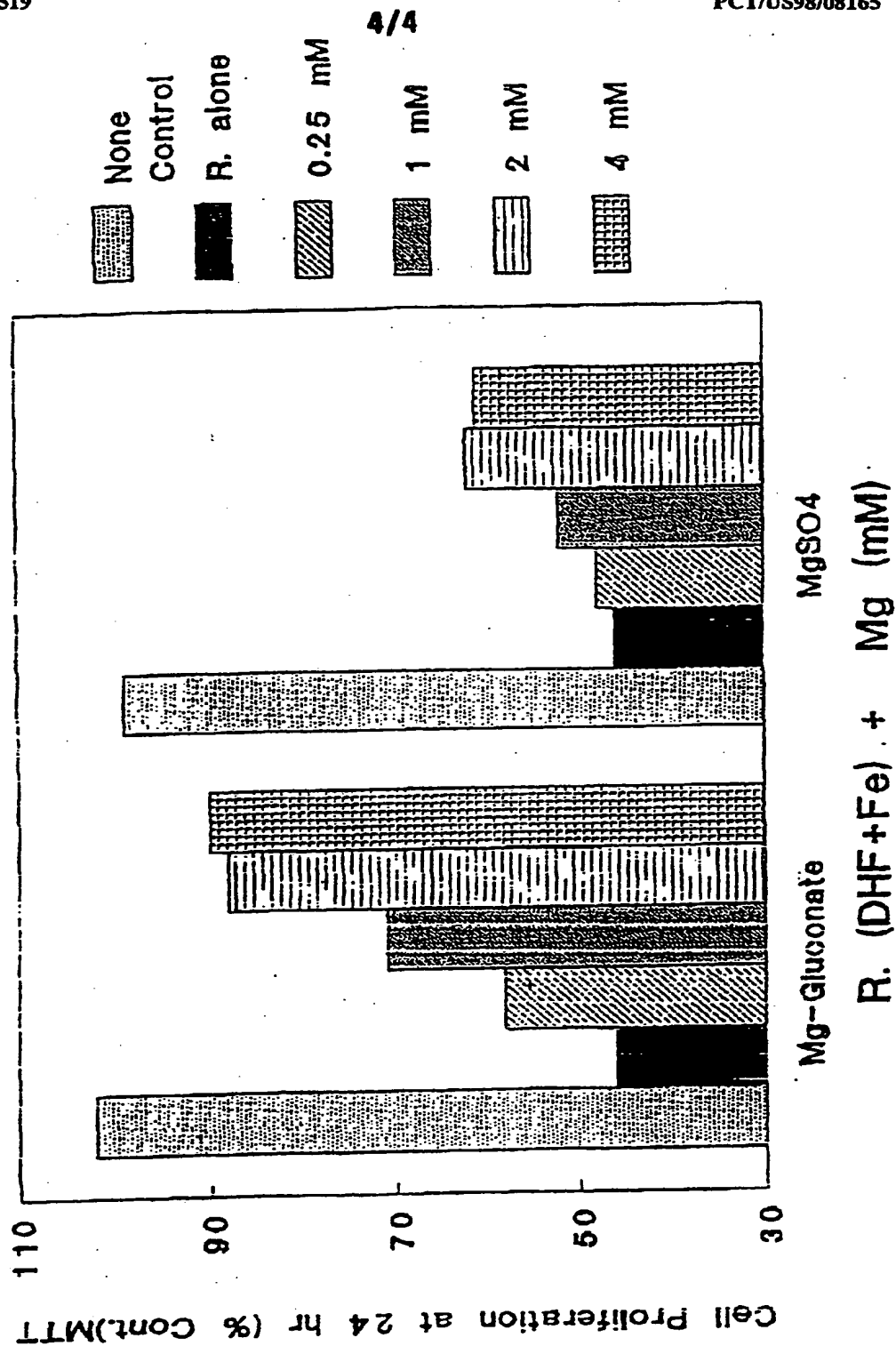


FIGURE 4.

# Effects of Mg-Gluconate & MgSO<sub>4</sub> on R.-induced loss of EC Proliferation





# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/08165

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K33/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 002 780 A (BAKTA GYOERGY ET AL) 26 March 1991 see column 1, line 22-40 - column 3, line 50-53; examples 1-10	1-6, 8-16
X	BUDAVARI ET AL.: "Merck Index" 1996, MERCK & CO, NEW JERSEY XP002075943 22078 see page 4464, column 2, paragraph 8 - page 4465, column 1, paragraph 7	1-6, 9-16
Y	BERKOW R.; FLETCHER A.: "Merck Manual" 1987, MERCK & CO, NEW JERSEY XP002075944 14658 see page 981, paragraph 5 - page 982, paragraph 7	1-6, 13-16
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

17 September 1998

Date of mailing of the international search report

02/10/1998

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## INTERNATIONAL SEARCH REPORT

Int. onal Application No

PCT/US 98/08165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REYNOLDS J.: "MARTINDALE - THE EXTRA PHARMACOPOEIA." 1996, ROYAL PHARMACEUTICAL SOCIETY, LONDON XP002076093 224540 see page 1171, column 1, paragraph 7 - paragraph 9 see page 1180, column 1, paragraph 6 - column 2, paragraph 3; table 2	1-6, 13-16
X	DE 35 17 916 A (KRUEGER GMBH & CO KG) 20 November 1986 see example 2	10-12, 19,20
X,P	BECKWITH M.C. ET AL: "Clinical implications of hypomagnesemia." JOURNAL OF PHARMACEUTICAL CARE IN PAIN AND SYMPTOM CONTROL, (1998) 6/1 (65-77). REFS: 33 ISSN: 1056-4950 CODEN: JPPSEX, XP002075939 United States see page 66, paragraph 2 - paragraph 4; tables 2-5	1-6, 13-16
X	KLEEFELD G: "MAGNESIUM GLUCONATE A MUSCLE RELAXANT." ANN OCUL 206 (10). 1973 (RECD 1974) 756 CODEN: ANOCAX ISSN: 0003-4371, XP002075940 see the whole document	1-6, 13-16
X	KLEEFELD G.: "Magnesium gluconate as muscle relaxant!. A PROPOS DU GLUCONATE DE MAGNESIUM, RELAXANT MUSCULAIRE. EN GUISE D'INTRODUCTION." BULL.SOC.BELGE OPHTAL., (1973) VOL 164 (229-240). CODEN: BBOPAX, XP002075941 see page 239, paragraph 7-8	1-6, 13-16
X	WO 87 01940 A (WISCONSIN ALUMNI RES FOUND) 9 April 1987 see claim 1; table 1	10-12, 19,20
X	EP 0 739 629 A (SHRIVASTAVA RAVI ;HYDROXYDASE SOCIETE DES EAUX M (FR)) 30 October 1996 see examples 3-6	10-12, 19,20
X	DE 39 40 315 A (STRATULAT SPERANTA DR MED) 13 June 1991 see abstract; claims 1-9; examples 3-6	1-7, 13-16
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# INTERNATIONAL SEARCH REPORT

Int'l. Application No  
PCT/US 98/08165

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>FISCHER W: "Contribution to the treatment of pasture tetany. Preliminary report on the administration of magnesium gluconate !. Beitrag zur Behandlung der Weidetetanie. Vorläufige Mitteilung über der Anwendung von Magnesiumgluconicum." DEUTSCHE TIERARZTLICHE WOCHENSCHRIFT, (1968 JAN 1) 75 (1) 8-11. JOURNAL CODE: ECS. ISSN: 0012-0847., XP002075942 GERMANY, WEST: Germany, Federal Republic of see abstract</p>	1-6, 13-16
X	<p>US 3 865 933 A (MUDGE CLIFTON F) 11 February 1975 see column 2, line 50-69; claims 1-3; example 1</p>	1,2

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/08165

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-9, 13-18  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 1-9, 13-18  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: -  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No  
PCT/US 98/08165

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